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STEPTOE & JOHNSON LLP
1330 CONNECTICUT AVENUE, N.W.
WASHINGTON, DC 20036

EXAMINER	
CROW, ROBERT THOMAS	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,081	ELLINGER ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,52-58 and 62-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25,52-58 and 62-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 7 July 2008 in which claim 1 was amended, no claims were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 1-25, 52-58, and 62-86 are under prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-7, 11, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duck et al (U.S. Patent No. 4,876,187, issued 24 October 1989) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000).

The following are new rejections necessitated by the amendments.

Regarding claim 1, Duck et al teach a probe array. In a single exemplary embodiment, Duck et al teach a probe molecule immobilized to a substrate (column 6, lines 15-67) wherein the probe is immobilized at one end and has a label at the other end (Figures 1-2). The probe is bound to a target followed by cleavage of a scissile linkage in the probe (Figure 1), wherein the resulting cleavage results in a first target region bound to a labeled first cleavage product of a first probe, which is noncovalently immobilized to the array surface via the hybridization to the target, wherein the target is in turn hybridized through a second target region to the second cleavage product of the probe, which is still immobilized on the surface of the array and is in the presence of a cleaving solution (bottom of Figure 1 and column 9, lines 50-65).

Duck et al do not explicitly teach two different probes on the array surface.

However, Koster et al teach a probe array comprising different sequences at different defined locations (Figure 3) in an ordered array (Figure 5). Koster et al also teach wherein the multiplexing, which requires a plurality of different probes, has the added advantage of allowing multiple simultaneous detection of targets and parallel

processing (column 4, lines 13-25). Thus, Koster et al teach the known technique of having multiple different sequences in an array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the surface of the array as taught by Duck et al so that the surface has multiple different sequences in an array to arrive at the instantly claimed array as taught by Koster et al with a reasonable expectation of success. Because the array has multiple different sequences, not all of the immobilized sequences would bind a single target. Because all of the probes on the array have the scissile linkage, the solution claves all of the probes, including at least a first probe that is bound to the target and at least a second probe that is not bound to a target. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an array having the added advantage of allowing multiple simultaneous detection of targets and parallel processing as explicitly taught by Koster et al (column 4, lines 13-25). In addition, it would have been obvious to the ordinary artisan that the known technique of using the multiple different sequences of Koster et al could have been applied to the array of Duck et al with predictable results because the multiple different sequences of Koster et al predictably result in an array useful for the detection of nucleic acid targets.

Regarding claims 2 and 3, the array of claim 1 is discussed above. Duck et al teach the first and second probes are oligonucleotides; namely, the probes are nucleic acids sequences (Abstract).

Regarding claim 4, the array of claim 3 is discussed above. Duck et al also teach the oligonucleotides have a length of from 10 to 100 bases (column 4, lines 1-10).

Regarding claim 5, the array of claim 1 is discussed above. Duck et al further teach the first cleavage product of the first probe molecule and the second cleavage product of the first probe molecule are approximately the same size; namely, Figure 1 shows the two fragments being approximately equal in size. The broadly claimed limitation "approximately equal in size" is interpreted to mean the cleavable linkage is in between the two ends due to the lack of explicit structural limitations on the number of bases or nucleotides in either cleavage product.

Regarding claim 6, the array of claim 1 is discussed above. It is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Thus, the teaching of Duck et al that the cleavage products **may** be enzymatically produced encompasses the alternate

embodiment wherein the cleavage products are **not** enzymatically produced. See MPEP § 2123 [R-5].

Regarding claim 7, the array of claim 1 is discussed above. Duck et al teach the cleavage is done by chemical methods; namely, basic conditions (column 11, lines 15-50).

Regarding claim 11, the array of claim 1 is discussed above. Duck et al teach the cleavage products are products of a nucleic acid of the formula A1-S-A2, wherein S is a nucleic acid that comprises the at least one selectively cleavable bond and A1 and A2 are any nucleic acids or nucleic acid analogs; namely, the cleavable linker S is between two nuclei acid sequences NA1 and NA2 (column 3, lines 40-60).

Regarding claim 15, the array of claim 1 is discussed above. Duck et al teach the label is a fluorescent label (column 4, lines 5-20).

Regarding claim 16, the array of claim 1 is discussed above. Duck et al teach the label is coupled to the probe molecules via an anchor group; namely, biotin is attached to the nucleic acid (column 4, lines 5-20). Biotin is an anchor group in accordance with the example listed in paragraph 0009 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding an "anchor" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

5. Claims 8-13 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duck et al (U.S. Patent No. 4,876,187, issued 24 October 1989) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claim 1 above, and further in view of Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998).

The following are new rejections necessitated by the amendments.

It is noted that while claim 11 has been broadly rejected under 35 U.S.C 103(a) as described above in Section 4, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 8-13, the array of claim 1 is discussed above in Section 4.

While Duck et al teach the cleavage products are products of chemical methods (i.e., under basic conditions, column 11, lines 15-50), and while Duck et al teach the scissile linkage is any selectively cleavable connecting chemical structure (column 4, lines 25-45), neither Duck et al nor Koster et al specifically teach functionally equivalent links cleaved by mercury ions (i.e., claims 8-9) or photolysis (i.e., claim 10), or the structures required by claims 12-13.

However, Monforte et al teach a probe array in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (column 38, lines 40-55 and column 15, lines 15-25). The probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array (column 15, lines 35-47). Cleavage of the functionally equivalent links is affected by

mercury ions (i.e., claims 8-9; column 22, lines 45-50) or by photolysis (i.e., claim 10; column 20, lines 1-5). Monforte et al also teach the cleavage products are products of cleavage of a nucleic acid of the formula A1-S-A2, wherein S is a nucleic acid that comprises the at least one selectively cleavable bond and A1 and A2 are any nucleic acids of nucleic acid analogs; namely, the cleavable linker is a phosphorothioate within a nucleoside dimer (i.e., claims 11-13; Figure 1I and column 19, lines 54-67). Monforte et al also teach the functionally equivalent cleavable links have the added advantage of being introduced at a selective position and are cleaved under conditions that do not permit cleavage of the immobilization attachment site (column 19, lines 40-55). Thus, Monforte et al teach the known technique of using the functionally equivalent cleavable links of the instant claims.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the probe array of Duck et al in view of Koster et al so that the cleavable links are the functionally equivalent links cleaved by mercury ions (i.e., claims 8-9) or photolysis (i.e., claim 10), and that the cleavable linker is in a probe A1-S-A2 wherein S is a nucleotide dimer (i.e., claims 11-12) having the structure required by claim 13 as taught by Monforte et al to arrive at the instantly claimed array with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an array having the added advantage of being introduced at a selective position and are cleaved under conditions that do not permit cleavage of the immobilization attachment site as explicitly taught by Monforte et al (column 19, lines

40-55). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent cleavable links as taught by Monforte et al could have been applied to the array of Duck et al in view of Koster et al with predictable results because the known technique of using the functionally equivalent cleavable links as taught by Monforte et al predictably results in cleavable links suitable for array based assays.

Regarding claim 52, the probe array of claim 1 is discussed above in Section 4.

It is noted that the preamble of this claim recites a "kit." The specification, however, does not define this term, and so it is being interpreted to encompass any collection of reagents that includes all of the elements of the claims. Any further interpretation of the word is considered an "intended use" and does not impart any further structural limitation of on the claimed subject matter. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "kit."

While Duck et al also teach reagents for the selective cleavage of the selectively cleavable bond in the probe molecules in the form of an RNAse (column 9, lines 20-50), a hybridization solution (column 8, lines 50-60), and washing (Figure 1 and Example 1), neither Duck et al nor Koster et al specifically teach the functionally equivalent hybridization or washing buffers.

However, Monforte et al also teach a collection of reagents (i.e., a kit) comprising reagents for the selective cleavage of the selectively cleavable bond in the probe molecules in the form of mercuric chloride (column 22, lines 45-50), a hybridization

buffer in the form of an annealing buffer (column 27, lines 17-30), and a washing buffer (column 27, lines 40-43). Monforte et al also teach buffers have the added advantage of being compatible with pH sensitive materials (column 29, lines 15-20). Thus, Monforte et al teach the known technique of providing functionally equivalent hybridization and washing buffers.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the kit of Duck et al in view of Koster et al so that hybridization and washing reagents are the functionally equivalent hybridization and washing buffers as taught by Monforte et al to arrive at the instantly claimed kit with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an kit having the added advantage of using functionally equivalent solutions being introduced at a selective position and are cleaved under conditions that are compatible with pH sensitive materials as explicitly taught by Monforte et al (column 29, lines 15-20). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent hybridization and washing buffers as taught by Monforte et al could have been applied to the kit of Duck et al in view of Koster et al with predictable results because the known technique of using the functionally equivalent hybridization and washing buffers as taught by Monforte et al predictably results in solutions suitable for array based assays.

Regarding claim 53, the kit of claim 52 is discussed above. Duck et al teach reagents in the form of RNAse(column 9, lines 20-50),, which is an enzyme.

Alternatively, regarding claims 53-54, the kit of claim 52 is discussed above. Monforte et al also teach heavy metal ions; namely, mercuric chloride for the cleavage of the functionally equivalent cleavable linkers of Monforte et al (column 22, lines 45-50). As noted above in the rejection of claims 8-13, Monforte et al also teach the functionally equivalent cleavable links of claims 8-13 have the added advantage of being introduced at a selective position and are cleaved under conditions that do not permit cleavage of the immobilization attachment site (column 19, lines 40-55). Thus, Monforte et al teach the known technique of using the functionally equivalent cleavable links of instant claims 8-13.

Thus, modification of the kit of Duck et al in view of Koster et al with the functionally equivalent cleavable links and cleavage reagents of Monforte et al results in a kit comprising the functionally equivalent cleavable links of instant claims 8-13 as well as mercuric chloride for the cleavage of the functionally equivalent cleavable linkers of Monforte et al (column 22, lines 45-50).

Regarding claim 55-58, the kit of claim 52 is discussed above. Monforte et al also teach a reaction chamber in the form of a Petri dish (i.e., claim 55; Example 2), a detection device in the form of a dual microchannel plate detector (i.e., claim 56; Example 4), a temperature control unit in the form of a thermocycler (i.e., claim 57; column 35, line 32), and that the probe array is in the form of a highly integrated autonomous unit; namely array is synthesized on a support in the form of a matrix (column 38, lines 40-55) and the solid support is a slide (Example 2). The array is integrated because the probes are attached to the slide, and autonomous because the

slide exists independently (i.e., claim 58). Thus, modification of the kit of Duck et al in view of Koster et al with the teachings of Monforte et al results in a kit having the limitations of claims 55-58.

6. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duck et al (U.S. Patent No. 4,876,187, issued 24 October 1989) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claim 1 above, and further in view of Nikiforov et al (U.S. Patent No. 5,518,900, issued 21 May 1996).

The following is a new rejection necessitated by the amendments.

Regarding claim 14, the array of claim 1 is discussed above in Section 4.

While Duck et al teach the cleavage products are products of chemical methods (i.e., under basic conditions, column 11, lines 15-50), and while Duck et al teach the scissile linkage is any selectively cleavable connecting chemical structure (column 4, lines 25-45), neither Duck et al nor Koster et al specifically teach the functionally equivalent phosphothioate linker.

However, Nikiforov et al teach the preferred use of the functionally equivalent phosphothioate bond in oligonucleotides, wherein the bonds have the added advantage of being exonuclease resistant (column 10, lines 25-50), which results in additional stability towards cellular extracts that may contain exonucleases. Thus, Nikiforov et al teach the known technique of using the functionally equivalent phosphothioate bond in oligonucleotides.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array the comprising cleavable linkers of Duck et al in view of Koster et al with the functionally equivalent cleavable phosphothioate bond to arrive at the instantly claimed invention as taught by Nikiforov et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would result in a probe array having the added advantage of having probes with additional stability towards cellular extracts that may contain exonucleases as a result of the functionally equivalent phosphothioate bonds being exonuclease resistant as explicitly taught by Nikiforov et al (column 2, lines 40-63 and Example VI). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent cleavable phosphothioate bond of Nikiforov et al could have been used for the cleavable bond of the array of Duck et al in view of Koster et al with predictable results because the functionally equivalent cleavable phosphothioate bond of Nikiforov et al predictably results in functionally equivalent cleavable bond.

7. Claims 17-18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duck et al (U.S. Patent No. 4,876,187, issued 24 October 1989) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claim 1 above, and further in view of Lockhart et al (U.S Patent No. 6,040,138, issued 21 March 2000).

The following are new rejections necessitated by the amendments.

Regarding claims 17-18, the array of claim 1 is discussed above in Section 4.

Neither Duck et al nor Koster et al teach third probe molecules (i.e., claim 17) or random sequences (i.e., claim 18).

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising a first probe molecule in the form of an oligonucleotide that hybridizes to a target (Abstract) and third (i.e., additional) probe molecules that have no selectively cleavable bond (i.e., claim 17); namely, mismatch control probes, wherein the mismatch control probe is an immobilized oligonucleotide (i.e., an ordinary, non-cleavable oligonucleotide; column 3, lines 30-40). The mismatch probes correspond to oligonucleotide probes (column 3, lines 30-40), which have defined sequences because the mismatch probes have deliberately selected sequences (i.e., claim 18; column 7, lines 20-22). Lockhart et al also teach the third probes have the added advantage that the third probe molecule (i.e., the mismatch probe) allows measurement of the concentration of hybridized material (column 17, lines 23-27). Thus, Lockhart et al teach the known technique of providing a third probe on the array (i.e., claim 17) that has a defined sequence (i.e., claim 18).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to have modified the array comprising immobilized probes of Duck et al in view of Koster et al with the additional third probe (i.e., claim 17) having a defined sequence (i.e., claim 18) as taught by Lockhart et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the

modification would have resulted in a probe array having the added advantage of allowing measurement of the concentration of hybridized material as explicitly taught by Lockhart et al (column 17, lines 23-27). In addition, it would have been obvious to the ordinary artisan that the known technique of providing the third defined sequence probe of Lockhart et al could have been used on the array of Duck et al in view of Koster et al with predictable results because the third defined sequence probe of Lockhart et predictably results in a probe useful for binding assays on arrays.

Regarding claims 22-23, the array of claims 1 is discussed above in Section 4.

While claims 22-23 are drawn to fourth probe molecules, the claims do not require third probe molecules. The instantly claimed fourth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claim 1.

While Duck et al teach labeled probes having cleavable linkers (Abstract), neither Duck et al nor Koster et al teach a fourth probe molecule which does not have affinity for targets (i.e., claim 22) that has a defined sequence (i.e., claim 23).

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target; Abstract) and fourth (i.e., additional) probe molecules having no specific affinity to target molecules; namely, expression level control probes, which are arranged on at least one array element because the probes are on the array (i.e., claim 22; column 3, lines 50-55). The fourth (i.e. additional) probes have a defined sequence because the expression control probes are complementary to known genes (i.e., claim 23; column 16, lines 55-61), and have the

added advantage that the fourth probes allows measurement of the overall health and metabolic activity of a cell, which allows a user to identify whether or not the results of a hybridization assay are due to a change in the amount of a target as a result of a change in the gene being studied or if the results are due to the general state of health of the cells from which the sample was isolated (column 16, lines 34-54).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Duck et al in view of Koster et al with the additional fourth probes (i.e., claim 22) having a defined sequence (i.e., claim 23) to arrive at the instantly claimed invention as taught by Lockhart et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of having a control for the overall health and metabolic activity of a cell, which aids in the interpretation of assay results, as explicitly taught by Lockhart et al (column 16, lines 34-54). In addition, it would have been obvious to the ordinary artisan that the known technique of providing the fourth defined sequence probe of Lockhart et al could have been used on the array of Duck et al in view of Koster et al with predictable results because the fourth defined sequence probe of Lockhart et predictably results in a probe useful for binding assays on arrays.

Regarding claims 24-25, the array of claim 1 is discussed above in Section 4.

While claims 24-25 are drawn to fifth probe molecules, the claims do not require fourth or third probe molecules. The instantly claimed fifth probe molecules are

therefore interpreted as a set of probes in addition to the probe molecules of claims 1 and 62.

While Duck et al teach probe molecules have at least one label (column 4, lines 5-20), at least one selectively cleavable bond between the site of their immobilization on the array surface and the label (Figure 1), Duck et al and Koster et al are silent with respect to fifth probe molecules which have affinity for spiking molecules (i.e., claim 24) or array elements distributed over the entire surface of the array on which said fifth probe molecules are located (i.e., claim 25).

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target (Abstract) and fifth (i.e., additional) probe molecules having no specific affinity to target molecules in the form of normalization controls (column 3, lines 50-55) arranged on at least one array element (e.g., on any position on the array; column 16, lines 36-31). The fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample; namely, the normalization controls hybridized to reference oligonucleotides added to the sample (i.e., claim 24; column 16, lines 1-4). Lockhart et al also teach array elements distributed over the entire surface of the array on which said fifth probe molecules are located; namely, the normalization probes are at multiple positions throughout the array (column 16, lines 26-31). Lockhart et al also teach the fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample in sufficient concentration to lead to a clearly detectable signal because

the normalization controls hybridized to reference oligonucleotides added to the sample so that a signal is obtained (i.e., claim 25; column 16, lines 1-4). The fifth probes also have the added advantage that the fifth probe molecule provides a control for variation is signals between arrays (column 16, lines 1-9). Thus, Lockhart et al teach the known technique of providing a fifth probe on the array (i.e., claim 24) and a specific affinity to spiking target molecules which are externally added (i.e., claim 25).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Duck et al in view of Koster et al with the additional fifth probes (i.e., claim 24) having a specific affinity to spiking target molecules which are externally added (i.e., claim 25) to arrive at the instantly claimed invention as taught by Lockhart et al et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of providing a control for variation is signals between arrays as explicitly taught by Lockhart et al (column 16, lines 1-9). In addition, it would have been obvious to the ordinary artisan that the known technique of providing the fifth defined sequence probe of Lockhart et al could have been used on the array of Duck et al in view of Koster et al with predictable results because the fifth defined sequence probe of Lockhart et predictably results in a probe useful for binding assays on arrays.

8. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duck et al (U.S. Patent No. 4,876,187, issued 24 October 1989) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claim 1 above, and further in view of Mackay et al (U.S. Patent No. 4,874,492, issued 17 October 1989).

The following is a new rejection necessitated by the amendments.

Regarding claim 19, the array of claim 1 is discussed above in Section 4.

Neither Duck et al nor Koster et al teach detectable units that are not linked to probe molecules.

However, Mackay et al teach arrays of polynucleotides in the form of 2-D gels (column 6, lines 56-67) having detectable units that are not attached to probe molecules; namely, calibration chemicals (column 6, lines 56-67), which have the added advantage of acting as calibration standards (column 6, lines 56-67). Thus, Mackay et al tech the known technique of providing arrays having detectable units not linked to probe molecules.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Duck et al in view of Koster et al to further comprise the detectable labels not attached to probes (i.e., calibration chemicals) to arrive at the instantly claimed invention as taught by Mackay et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having standardized calibration as explicitly taught by Mackay et al (column 6, lines 56-67). In addition, it would have been obvious to the ordinary artisan

that the known technique of providing probe independent detectable labels of Mackay et al could have been used on the array of Duck et al in view of Koster et al with predictable results because the probe independent detectable labels of Mackay et al predictably result in a labels useful for calibrating arrays.

9. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duck et al (U.S. Patent No. 4,876,187, issued 24 October 1989) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) in view of Lockhart et al (U.S Patent No. 6,040,138, issued 21 March 2000) as applied to claim 17 above, and further in view of Kievits et al (U.S. Patent No. 5,770,360, issued 23 June 1998).

The following is a new rejection necessitated by the amendments.

Regarding claims 20, the array of claim 17 is discussed above in Section 7.

Neither Duck et al Koster et al, nor Lockhart et al teach different degrees in labeling.

However, Kievits et al teach immobilized oligonucleotides comprising a plurality of different probes, wherein the additional (i.e., second) probe molecules are arranged on different array elements; namely, two different oligonucleotide probes are arranged in two different spots (column 5, lines 17-50). The probes are labeled differently (column 5, lines 32-37); therefore, the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Kievits et al teach the differential labeling has the added advantage of allowing indication of whether a test result is positive or negative (column 5, lines 17-44), thereby excluding false negatives

(column 2, lines 1-9). Thus, Kievits et al teach the known technique of differential labeling.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Duck et al in view of Koster et al and Lockhart et al so that the third probe has a different degree of labeling to arrive at the instantly claimed invention as taught by Kievits et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing indication of whether a test result is positive or negative, thereby excluding false negatives, as explicitly taught by Kievits et al (column 2, lines 1-9 and column 5, lines 17-44). In addition, it would have been obvious to the ordinary artisan that the known technique of differential labeling of Kievits et al could have been used on the array of Duck et al in view of Koster et al and Lockhart et al with predictable results because the differential labeling of Kievits et al predictably result in a labels useful for eliminating false negatives on arrays.

10. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duck et al (U.S. Patent No. 4,876,187, issued 24 October 1989) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) in view of Mackay et al (U.S. Patent No. 4,874,492, issued 17 October 1989) as applied to claim 19 above, and further in view of Kievits et al (U.S. Patent No. 5,770,360, issued 23 June 1998).

The following is a new rejection necessitated by the amendments.

Regarding claim 21, the array of claim 19 is discussed above in Section 8.

Neither Duck et al, Koster et al, nor Mackay et al teach different degrees in labeling.

However, Kievits et al teach immobilized oligonucleotides comprising a plurality of different probes, wherein the additional (i.e., second) probe molecules are arranged on different array elements; namely, two different oligonucleotide probes are arranged in two different spots (column 5, lines 17-50). The probes are labeled differently (column 5, lines 32-37); therefore, the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Kievits et al teach the differential labeling has the added advantage of allowing indication of whether a test result is positive or negative (column 5, lines 17-44), thereby excluding false negatives (column 2, lines 1-9). Thus, Kievits et al teach the known technique of differential labeling.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Duck et al in view of Koster et al and Mackay et al so that the different array elements have the different degree of labeling to arrive at the instantly claimed invention as taught by Kievits et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing indication of whether a test result is positive or negative, thereby excluding false negatives, as explicitly taught by Kievits et al (column 2, lines 1-9 and column 5, lines 17-44). In addition, it would have been

obvious to the ordinary artisan that the known technique of differential labeling of Kievits et al could have been used on the array of Duck et al in view of Koster et al and Mackay et al with predictable results because the differential labeling of Kievits et al predictably result in a labels useful for eliminating false negatives on arrays.

11. Claims 62-74 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000).

Regarding claim 62, Monforte et al teach a probe array. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (column 38, lines 40-55 and column 15, lines 15-25). The probe molecules have at least one label because the primers are labeled (column 15, lines 35-47), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array (column 15, lines 35-47).

Monforte et al further teach the primers comprising the cleavable bond are hybridized to a single stranded target nucleic acid (column 6, lines 15-28). Monforte et al also teach that the molecules are subjected to a cleavage step (column 8, lines 65-column 9, line 17); thus, the cleavable molecules are bound to a target and are in contact with a cleavage solution.

While Monforte et al teach the formulation of an array of the immobilized, cleavable primers (column 38, lines 40-55 and column 15, lines 15-25), that the probes are immobilized to the array surface at any stage (column 7, lines 40-50), and the use of probes for multiplexing (column 41, lines 20-50), which requires a plurality of different probes, Monforte et al do not explicitly teach two different probes on the array surface.

However, Koster et al teach a probe array comprising different sequences at different defined locations (Figure 3) in an ordered array (Figure 5). Koster et al also teach wherein the multiplexing, which requires a plurality of different probes, has the added advantage of allowing multiple simultaneous detection of targets and parallel processing (column 4, lines 13-25). Thus, Koster et al teach the known technique of having multiple different sequences in an array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the array comprising immobilized primers for multiplexing as taught by Monforte et al to have multiple different sequences in the array to arrive at the instantly claimed array as taught by Koster et al with a reasonable expectation of success. Because the array has multiple different sequences, not all of the immobilized sequences would bind a single target. Thus, when the solution is added but before cleavage has commenced, at least one probe is bound to the target, at least a second probe is not bound to a target, and both probes still have labels thereon because cleavage has yet to commence. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an array having the added advantage of allowing multiple simultaneous

detection of targets and parallel processing as explicitly taught by Koster et al (column 4, lines 13-25). In addition, it would have been obvious to the ordinary artisan that the known technique of using the multiple different sequences of Koster et al could have been applied to the array of Monforte et al with predictable results because the multiple different sequences of Koster et al predictably result in an array useful for the detection of nucleic acid targets.

Regarding claims 63 and 64, the array of claim 62 is discussed above. Monforte et al teach the first and second probes are oligonucleotides; namely, the probes are oligonucleotide primers (column 4, lines 22-40).

Regarding claim 65, the array of claim 64 is discussed above. Monforte et al also teach the oligonucleotides have a length of from 10 to 100 bases; namely, ten nucleotides (column 15, lines 35-50).

Regarding claim 66, the array of claim 62 is discussed above. Monforte et al further teach the first cleavage product of the first probe molecule and the second cleavage product of the first probe molecule are approximately the same size; namely, the probe is ten nucleotides (column 15, lines 35-50), and the cleavable site is within 5 nucleotides of the end (column 19, lines 40-55).

Regarding claim 67, the array of claim 62 is discussed above. Monforte et al teach the selectively cleavable bond cannot be selectively cleaved by enzymatic methods; namely, the cleavable link is chemically cleavable (column 19, lines 54-67), but not enzymatically cleavable.

Regarding claim 68, the array of claim 62 is discussed above. Monforte et al also teach the selectively cleavable bond can be cleaved by chemical methods (column 19, lines 54-67).

Regarding claims 69 and 70, the array of claim 62 is discussed above. Monforte et al further teach the selectively cleavable bond can be selectively cleaved by the mercury ions (column 22, lines 45-50).

Regarding claim 71, the array of claim 62 is discussed above. Monforte et al teach the selectively cleavable bond can be cleaved by photolysis (column 20, lines 1-5).

Regarding claims 72-74, the array of claim 62 is discussed above. Monforte et al also teach the probe molecules comprise a nucleic acid of the formula A1-S-A2, wherein S is a nucleic acid that comprises the at least one selectively cleavable bond and A1 and A2 are any nucleic acids of nucleic acid analogs; namely, the cleavable linker is a phosphorothioate within a nucleoside dimer (Figure 1I and column 19, lines 54-67).

Regarding claim 76, the array of claim 62 is discussed above. Monforte et al also teach the label is a detectable label and is fluorescent (column 15, lines 35-50). Fluorescent labels are detectable by labeled reporter probes because signal generating antibodies to the fluorescent labels can be obtained.

12. Claim 75 is rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claim 62 above, and further in view of Nikiforov et al (U.S. Patent No. 5,518,900, issued 21 May 1996).

Regarding claim 75, the array of claim 62 is discussed above in Section 11.

While Monforte et al teach a number of thiolated nucleotides (Figures 1H, 1I, and 1P), neither Monforte et al nor Koster et al teach the functionally equivalent phosphothioate linker.

However, Nikiforov et al teach the preferred use of the functionally equivalent phosphothioate bond in oligonucleotides, wherein the bonds have the added advantage of being exonuclease resistant (column 10, lines 25-50), which results in additional stability towards cellular extracts that may contain exonucleases. Thus, Nikiforov et al teach the known technique of using the functionally equivalent phosphothioate bond in oligonucleotides.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array the comprising cleavable linkers of Monforte et al in view of Koster et al so that the cleavable link is the functionally equivalent cleavable phosphothioate bond to arrive at the instantly claimed invention as taught by Nikiforov et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would result in a probe array having the added advantage of having probes with additional stability towards cellular extracts that may contain exonucleases as a

result of the functionally equivalent phosphothioate bonds being exonuclease resistant as explicitly taught by Nikiforov et al (column 2, lines 40-63 and Example VI). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent cleavable phosphothioate bond of Nikiforov et al could have been used for the cleavable bond of the array of Monforte et al in view of Koster et al with predictable results because the functionally equivalent cleavable phosphothioate bond of Nikiforov et al predictably results in functionally equivalent cleavable bond.

13. Claim 77 is rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claims 62 and 76 above, and further in view of Fung et al (U.S. Patent No. 4,757,141, issued 12 July 1988).

Regarding claim 77, the array of claims 62 and 76 is discussed above in Section 11.

Neither Monforte et al nor Koster et al teach anchor groups.

However, Fung et al teach the attachment of fluorescent labels (i.e., dyes) to probe molecules (i.e., oligonucleotides) using anchor groups (i.e., linkers; Abstract) with the added advantage that the linkers attach the label using automated methods in high yield (i.e., 95%; column 2, lines 40-63 and Example VI). Thus, Fung et al teach the known technique of using anchor groups to attach fluorescent labels to oligonucleotides.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array comprising labels of

Monforte et al in view of Koster et al so further comprise the anchor groups (i.e., linkers) to arrive at the instantly claimed invention as taught by Fung et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would result in a probe array that is readily labeled using automated method in high yield as explicitly taught by Fung et al (column 2, lines 40-63 and Example VI). In addition, it would have been obvious to the ordinary artisan that the known technique of using the anchor of Fung et al could have been used to attach the fluorescent labels of Monforte et al in view of Koster et al with predictable results because the anchor of Fung et al predictably results in reliable method of attaching a label on an oligonucleotide.

14. Claims 78-79, and 83-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claim 62 above, and further in view of Lockhart et al (U.S Patent No. 6,040,138, issued 21 March 2000).

Regarding claims 78-79, the array of claim 62 is discussed above in Section 11.

Neither Monforte et al nor Koster et al teach third probe molecules (i.e., claim 78) or random sequences (i.e., claim 79).

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising a first probe molecule in the form of an oligonucleotide that hybridizes to a target (Abstract) and third (i.e., additional)

probe molecules that have no selectively cleavable bond (i.e., claim 78); namely, mismatch control probes, wherein the mismatch control probe is an immobilized oligonucleotide (i.e., an ordinary, non-cleavable oligonucleotide; column 3, lines 30-40). The mismatch probes correspond to oligonucleotide probes (column 3, lines 30-40), which have defined sequences because the mismatch probes have deliberately selected sequences (i.e., claim 79; column 7, lines 20-22). Lockhart et al also teach the third probes have the added advantage that the third probe molecule (i.e., the mismatch probe) allows measurement of the concentration of hybridized material (column 17, lines 23-27). Thus, Lockhart et al teach the known technique of providing a third probe on the array (i.e., claim 78) that has a defined sequence (i.e., claim 79).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to have modified the array comprising immobilized probes of Monforte et al in view of Koster et al with the additional third probe (i.e., claim 78) having a defined sequence (i.e., claim 79) as taught by Lockhart et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing measurement of the concentration of hybridized material as explicitly taught by Lockhart et al (column 17, lines 23-27). In addition, it would have been obvious to the ordinary artisan that the known technique of providing the third defined sequence probe of Lockhart et al could have been used on the array of Monforte et al in view of Koster

et al with predictable results because the third defined sequence probe of Lockhart et predictably results in a probe useful for binding assays on arrays.

Regarding claims 83-84, the array of claim 62 is discussed above in Section 11.

While claims 83-84 are drawn to fourth probe molecules, the claims do not require third probe molecules. The instantly claimed fourth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claim 62.

While Monforte et al teach labeled probes having cleavable linkers (column 9, lines 5-10), neither Monforte et al nor Koster et al teach a fourth probe molecule which does not have affinity for targets (i.e., claim 83) that has a defined sequence (i.e., claim 84).

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target; Abstract) and fourth (i.e., additional) probe molecules having no specific affinity to target molecules; namely, expression level control probes, which are arranged on at least one array element because the probes are on the array (i.e., claim 83; column 3, lines 50-55). The fourth (i.e. additional) probes have a defined sequence because the expression control probes are complementary to known genes (i.e., claim 84; column 16, lines 55-61), and have the added advantage that the fourth probes allows measurement of the overall health and metabolic activity of a cell, which allows a user to identify whether or not the results of a hybridization assay are due to a change in the amount of a target as a result of a

change in the gene being studied or if the results are due to the general state of health of the cells from which the sample was isolated (column 16, lines 34-54).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al in view of Koster et al with the additional fourth probes (i.e., claim 83) having a defined sequence (i.e., claim 84) to arrive at the instantly claimed invention as taught by Lockhart et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of having a control for the overall health and metabolic activity of a cell, which aids in the interpretation of assay results, as explicitly taught by Lockhart et al (column 16, lines 34-54). In addition, it would have been obvious to the ordinary artisan that the known technique of providing the fourth defined sequence probe of Lockhart et al could have been used on the array of Monforte et al in view of Koster et al with predictable results because the fourth defined sequence probe of Lockhart et predictably results in a probe useful for binding assays on arrays.

Regarding claim 85-86, the array of claim 62 is discussed above.

While claims 85-86 are drawn to fifth probe molecules, the claims do not require fourth or third probe molecules. The instantly claimed fifth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claim 62.

While Monforte et al teach probe molecules have at least one label (column 9, lines 5-10), at least one selectively cleavable bond between the site of their

immobilization on the array surface and the label (i.e., the label is in a fragment of the probe that is releasable from the array; column 9, lines 5-10), Monforte et al are silent with respect to fifth probe molecules which have affinity for spiking molecules (i.e., claim 85) or array elements distributed over the entire surface of the array on which said fifth probe molecules are located (i.e., claim 86).

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target (Abstract) and fifth (i.e., additional) probe molecules having no specific affinity to target molecules in the form of normalization controls (column 3, lines 50-55) arranged on at least one array element (e.g., on any position on the array; column 16, lines 36-31). The fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample; namely, the normalization controls hybridized to reference oligonucleotides added to the sample (i.e., claim 85; column 16, lines 1-4). Lockhart et al also teach array elements distributed over the entire surface of the array on which said fifth probe molecules are located; namely, the normalization probes are at multiple positions throughout the array (column 16, lines 26-31). Lockhart et al also teach the fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample in sufficient concentration to lead to a clearly detectable signal because the normalization controls hybridized to reference oligonucleotides added to the sample so that a signal is obtained (i.e., claim 86; column 16, lines 1-4). The fifth probes also have the added advantage that the fifth probe molecule provides a control for variation

is signals between arrays (column 16, lines 1-9). Thus, Lockhart et al teach the known technique of providing a fifth probe on the array (i.e., claim 85) and a specific affinity to spiking target molecules which are externally added (i.e., claim 86).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al with the additional fifth probes (i.e.,, claim 85) having a specific affinity to spiking target molecules which are externally added (i.e., claim 86) to arrive at the instantly claimed invention as taught by Lockhart et al et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of providing a control for variation is signals between arrays as explicitly taught by Lockhart et al (column 16, lines 1-9). In addition, it would have been obvious to the ordinary artisan that the known technique of providing the fifth defined sequence probe of Lockhart et al could have been used on the array of Monforte et al in view of Koster et al with predictable results because the fifth defined sequence probe of Lockhart et predictably results in a probe useful for binding assays on arrays.

15. Claim 80 is rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claim 62 above, and further in view of Mackay et al (U.S. Patent No. 4,874,492, issued 17 October 1989).

Regarding claim 80, the array of claim 62 is discussed above in Section 11.

Neither Monforte et al nor Koster et al teach detectable units that are not linked to probe molecules.

However, Mackay et al teach arrays of polynucleotides in the form of 2-D gels (column 6, lines 56-67) having detectable units that are not attached to probe molecules; namely, calibration chemicals (column 6, lines 56-67), which have the added advantage of acting as calibration standards (column 6, lines 56-67). Thus, Mackay et al tech the known technique of providing arrays having detectable units not linked to probe molecules.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al in view of Koster et al with the detectable labels not attached to probes (i.e., calibration chemicals) to arrive at the instantly claimed invention as taught by Mackay et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having standardized calibration as explicitly taught by Mackay et al (column 6, lines 56-67). In addition, it would have been obvious to the ordinary artisan that the known technique of providing probe independent detectable labels of Mackay et al could have been used on the array of Monforte et al in view of Koster et al with predictable results because the probe independent detectable labels of Mackay et al predictably result in a labels useful for calibrating arrays.

16. Claim 81 is rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) in view of Lockhart et al (U.S Patent No. 6,040,138, issued 21 March 2000) as applied to claim 78 above, and further in view of Kievits et al (U.S. Patent No. 5,770,360, issued 23 June 1998).

Regarding claim 81, the array of claim 78 is discussed above in Section 14.

Neither Monforte et al, Koster et al, nor Lockhart et al teach different degrees in labeling.

However, Kievits et al teach immobilized oligonucleotides comprising a plurality of different probes, wherein the additional (i.e., second) probe molecules are arranged on different array elements; namely, two different oligonucleotide probes are arranged in two different spots (column 5, lines 17-50). The probes are labeled differently (column 5, lines 32-37); therefore, the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Kievits et al teach the differential labeling has the added advantage of allowing indication of whether a test result is positive or negative (column 5, lines 17-44), thereby excluding false negatives (column 2, lines 1-9). Thus, Kievits et al teach the known technique of differential labeling.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al in view of Koster et al and Lockhart et al so that the third probe has the different degree of labeling to arrive at the instantly claimed invention as taught by Kievits et al with a

reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing indication of whether a test result is positive or negative, thereby excluding false negatives, as explicitly taught by Kievits et al (column 2, lines 1-9 and column 5, lines 17-44). In addition, it would have been obvious to the ordinary artisan that the known technique of differential labeling of Kievits et al could have been used on the array of Monforte et al in view of Koster et al and Lockhart et al with predictable results because the differential labeling of Kievits et al predictably result in a labels useful for eliminating false negatives on arrays.

17. Claim 82 is rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) in view of Mackay et al (U.S. Patent No. 4,874,492, issued 17 October 1989) as applied to claim 80 above, and further in view of Kievits et al (U.S. Patent No. 5,770,360, issued 23 June 1998).

Regarding claim 82, the array of claim 80 is discussed above in Section 15.

Neither Monforte et al, Koster et al, nor Mackay et al teach different degrees in labeling.

However, Kievits et al teach immobilized oligonucleotides comprising a plurality of different probes, wherein the additional (i.e., second) probe molecules are arranged on different array elements; namely, two different oligonucleotide probes are arranged in two different spots (column 5, lines 17-50). The probes are labeled differently

(column 5, lines 32-37); therefore, the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Kievits et al teach the differential labeling has the added advantage of allowing indication of whether a test result is positive or negative (column 5, lines 17-44), thereby excluding false negatives (column 2, lines 1-9). Thus, Kievits et al teach the known technique of differential labeling.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al in view of Koster et al and Mackay et al with the different degree of labeling to arrive at the instantly claimed invention as taught by Kievits et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing indication of whether a test result is positive or negative, thereby excluding false negatives, as explicitly taught by Kievits et al (column 2, lines 1-9 and column 5, lines 17-44). In addition, it would have been obvious to the ordinary artisan that the known technique of differential labeling of Kievits et al could have been used on the array of Monforte et al in view of Koster et al and Mackay et al with predictable results because the differential labeling of Kievits et al predictably result in a labels useful for eliminating false negatives on arrays.

Response to Arguments

18. Applicant's arguments filed 7 July 2008 (i.e., the "Remarks") have been fully considered but they are not persuasive for the reason(s) listed below.

A. Applicant's arguments with respect to the previous rejections of claims 1-25 and 52-58 have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

B. With respect to independent claim 62, Applicant presents the following arguments:

I. Applicant argues on page 16 of the Remarks that Applicant's oligonucleotides as illustrated in Figure 7 of the instant specification, one strand remains cleaved and the other remains uncleaved, thus immobilizing the labeled cleavage product.

II. Applicant further argues on pages 16-17 of the Remarks that Figure 16 of Monforte et al shows that both strands are cleaved, which makes a portion of the immobilized strand after cleavage, and further argues that the first cleavage product (i.e., the end of the cleaved probe) is not immobilized.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., one uncleaved strand or cleavage products) are not recited in claim 62 Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057

(Fed. Cir. 1993). Claim 62 merely requires probes having selectively cleavable bonds, and does not require any actual cleavage products.

Thus, none of the arguments presented above regarding cleavage products apply to independent claim 62, or claims 63-86, which depend upon claim 62

C. Applicant also argues on page 17 of the Remarks that Koster et al does not teach a cleavage product of a second probe molecule immobilized on an array surface,

However, as noted above, Koster et al are not relied upon for the teaching of cleavage products. Rather, Koster et al are relied upon for multiple different probes on the same array surface.

Thus, as detailed in the rejections presented above, modification of the array of Monforte et al with the teachings of Koster et al results in an array having multiple different sequences, each having a cleavable bond. Because the array has multiple different sequences, not all of the immobilized sequences would bind a single target. Thus, when the solution is added but before cleavage has commenced, at least one probe is bound to the target, at least a second probe is not bound to a target, and both probes still have labels thereon because cleavage has yet to commence. Claim 62 is therefore obvious over the prior art.

D. As noted above, Applicant's remaining arguments regarding claims 1-25 and 52-58 have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments. Applicant's remaining arguments regarding claims 62-86 rely on the arguments regarding the alleged deficiencies of Monforte et al in view

of Koster et al. These arguments are considered above. Because the arguments regarding the alleged deficiencies of Monforte et al in view of Koster et al were not persuasive, the rejections of the dependent claims are maintained for the reasons detailed above.

Conclusion

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

21. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-

1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert T. Crow/
Examiner, Art Unit 1634

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634

Robert T. Crow
Examiner
Art Unit 1634